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Synthesis of 2-aminopyridine Lactones and Studies of Their Antioxidant, Antibacterial and Antifungal Properties †

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Abstract: In the present work, the synthesis and biological activities of substituted 2-aminopyridine δ -lactone derivatives were achieved. 4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carbonitrile was synthesised from 4-hydroxy-4-methylpentan-2-one, followed by its transformation in enaminonitrile with DMFDMA. The antioxidant effects of substituted 2-aminopyridine δ -lactone derivatives were evaluated through DPPH assay and revealed a great antioxidant capacity. The antifungal and antibacterial activities were investigated by disc diffusion method against clinical Gram-negative bacteria and against clinical fungi. The study shows moderate to very good antibacterial and antifungal activities for the new substituted 2-aminopyridine δ -lactone derivatives.

Keywords: 2-aminopyridines; bis-2-aminopyridines; antioxidant; DPPH; radical scavenger; antibacterial activity; antifungal activity

1. Introduction

Substituted 2-aminopyridine δ -lactone derivatives were achieved. 4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carbonitrile (**1**) was synthesised from 4-hydroxy-4-methylpentan-2-one [**2**] (Figure 1), followed by its transformation in enaminonitrile with DMFDMA [**1**].

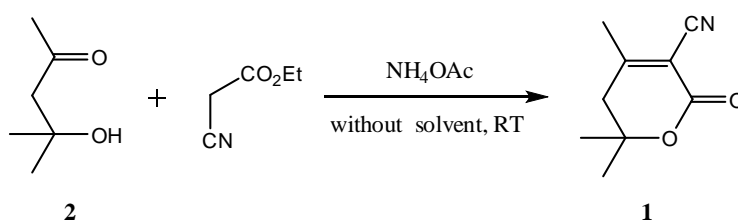


Figure 1. Synthesis of 4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carbonitrile **1**.

The compound **3** was prepared by the reaction of δ -lactone nitrile «4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carbonitrile» **1** with dimethylformamide dimethylacetal DMFDMA in stoichiometric amounts. The reaction was performed at room temperature during 24 h and afforded good overall yield (72%) [**1**] according the Figure 2.

The reaction of enaminolactone nitrile **3** and primary amines **4a–f** in refluxed DMF according to our previous work [**1**] results in new substituted 2-aminopyridines **5a–f**, according Figure 3, results are reported in Table 1.

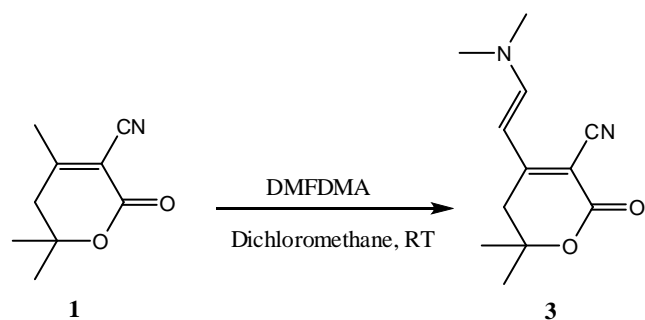


Figure 2. Synthesis of enaminolactone nitrile 3.

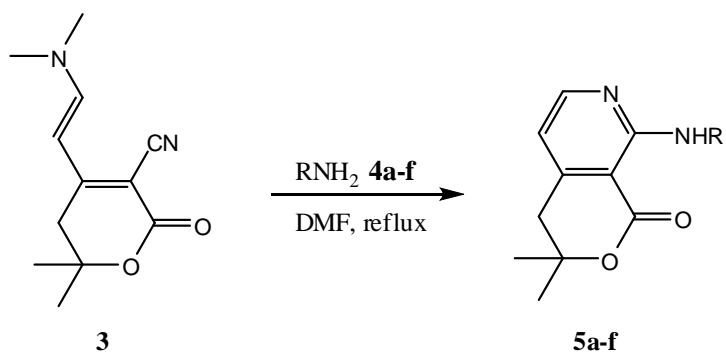


Figure 3. Synthesis of 2-aminopyridines 5a-f from enaminolactone nitrile 3.

The reactions between 1 equiv of diamines **6a–c** with 2 equiv of enaminolactone nitrile **3** were performed. The mixture was refluxed in DMF during 6 h. After removing of the solvent and purification by column chromatography, we afforded the new original bis-(2-aminopyridines) **7a–c** in moderate to good yields (Figure 4, Table 2).

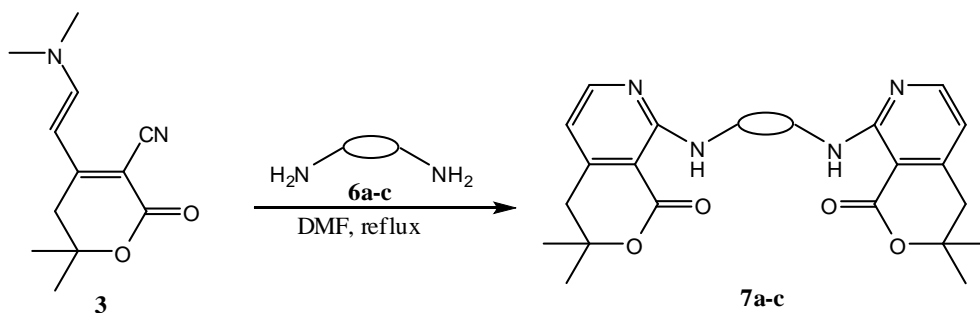
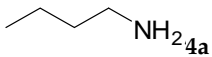
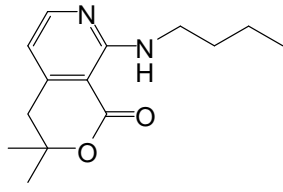
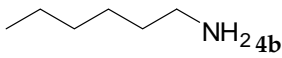
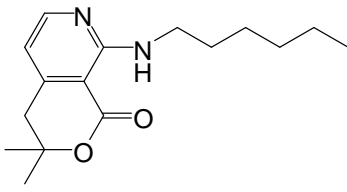
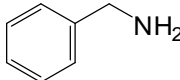
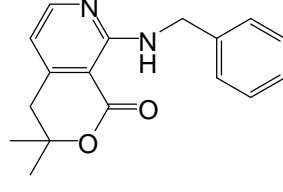
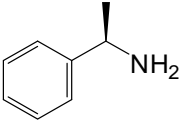
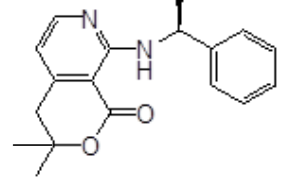
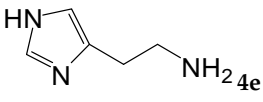
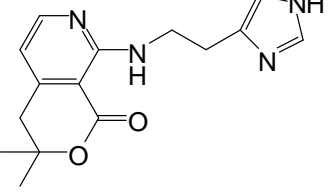
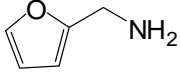
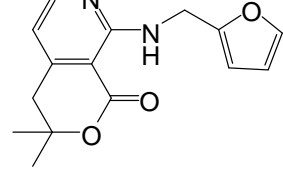


Figure 4. Synthesis of new bis-(2-aminopyridines) **7a–c**.

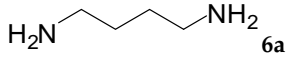
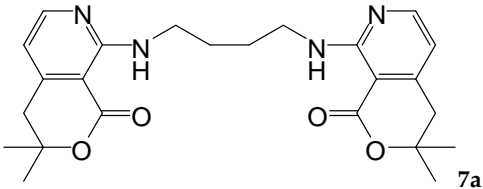
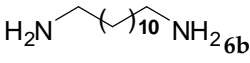
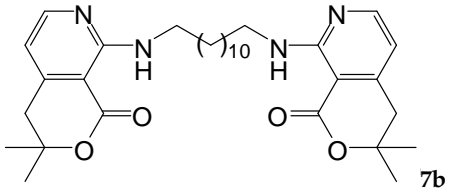
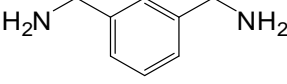
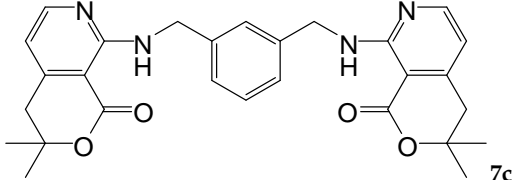
The structure of the compounds **7a–c** was confirmed by spectral data (IR, ^1H NMR and ^{13}C NMR).

Table 1. Synthesis of 2-aminopyridine lactones.

Entry	Enaminolactone	RNH ₂	Product	Yield (%)
1	3	 4a	 5a	95
2	3	 4b	 5b	87
3	3	 4c	 5c	92
4	3	 4d	 5d	96
5	3	 4e	 5e	95
6	3	 4f	 5f	96

The structure of substituted 2-aminopyridine δ -lactones were characterised by spectroscopic methods (IR, ¹H NMR, ¹³C NMR and MS).

Table 2. Synthesis of bis-2-aminopyridine lactones.

Entry	RNH ₂	Product	Yield (%)
1	 6a	 7a	57
2	 6b	 7b	60
3	 6c	 7c	89

2. Antioxidant Effects

The antioxidant effects of substituted 2-aminopyridine δ -lactone derivatives were evaluated through DPPH assay and revealed a great antioxidant capacity.

For initial screening of antioxidant activity DPPH on TLC was employed [2]. After the qualitative confirmation of antioxidant potential, spectroscopic measurements were made through DPPH assay. The antioxidant properties were measured and evidenced in terms of their efficient concentration IC₅₀, as well as their reduction kinetics [3]. Evaluation of the antioxidant activity by the test of DPPH, revealed a great antioxidant capacity for the most of compounds tested with a variation of IC₅₀ between 1.30–3.61 mg/mL and times of reaction of 30 min.

3. Antifungal and Antibacterial Activities

The antifungal and antibacterial activities of 2-aminopyridines and bis-2-aminopyridines were investigated in vitro in order to evaluate their efficacy. The antibacterial activity of the compounds was determined by the disc diffusion method [4,5] against clinical Gram-negative bacteria: *Escherichia coli*, *Pseudomonas aeruginosa* and Gram-positive bacteria: *Staphylococcus aureus*, *Listeria monocytogenes* and *Bacillus cereus*. The antifungal activity of the compounds was determined by using a direct-contact and agar diffusion test [4] against clinical fungi *Aspergillus flavus* and *Aspergillus ochraceus*. The compounds showed moderate to very good antibacterial and antifungal activities, that the 5b, 5d, 5e and 5f presents a best minimal inhibitory concentration (MIC) with 62.5 μ g/mL. The *Aspergillus ochraceus* strain revealed a stronger sensitivity than *Aspergillus flavus* to all compounds tested, While that the 7c and 7b showed a broad-spectrum antifungal activity against pathogenic *Aspergillus ochraceus* with an inhibition percentage of 77% and 78%, respectively. Based our results, the compounds of 2-aminopyridines and bis-2-aminopyridines can be considered as a source of novel antibiotic and antifungal.

4. Experimental

In the supplementary informations:

- Synthesis and Screening of Antioxidant Potential
- Screening of antibacterial and antifungal properties of the compounds.

5. Conclusions

The study shows moderate to very good antibacterial and antifungal activities for the new substituted 2-aminopyridine δ -lactone derivatives.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/ecsoc-25-11709/s1>.

Author Contributions: Conceptualization, D.V.; Investigation, F.S. and N.B.; Writing—Original draft, N.B. and D.V.; Writing—Review and editing, N.C., N.B. and D.V. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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